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REVIEW

Systemic Adjuvant Therapy of Breast Cancer

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Systematic adjuvant therapy has improved the outcome for women with operable breast cancer. As a result, a substantial proportion of patients with this disease are candidates for adjuvant treatment. In providing a woman with recommendations for therapy, her risk of developing recurrent breast cancer needs to be assessed in relationship to the degree of benefit she will obtain from treatment. With the range of presently available treatments, an individualized approach is necessary to provide the patient with options appropriate for her own situation. For women with a high risk of recurrence despite current standard adjuvant therapies, innovative approaches with high dose chemotherapy followed by infusion of autologous hematopoietic stem cells and growth factors are being evaluated. Ongoing clinical trials will demonstrate whether or not these newer therapies result in a better outcome. J. Surg. Oncol. 64:167–172

KEY WORDS: breast cancer; adjuvant treatment; tamoxifen; chemotherapy; breast cancer prognosis

INTRODUCTION

The development of effective systemic adjuvant therapies for women with operable breast cancer is a major advance in the treatment of this common malignancy. Women with breast cancer treated in the era following the introduction of adjuvant therapy into standard practice have a superior outcome compared to women from earlier times [1]. A meta-analysis incorporating clinical trials from many countries has demonstrated improved survival for women who received adjuvant therapy [2]. As a result of these and other studies, the majority of women with invasive breast cancer diagnosed in the United States are now considered to be candidates for adjuvant therapy. The specific recommendations given to patients have evolved as information from clinical trials has entered the medical literature and will continue to change as ongoing studies are completed. In this review we provide guidelines for decision making recognizing that the unfolding nature of the medical literature can lead to a range of opinions.

Although the outcome for women with operable breast cancer has improved with adjuvant therapy, many still die of recurrent breast cancer. Thus new adjuvant programs are necessary, particularly for those women who are at a high risk for metastatic disease. This review concludes with a consideration of high dose chemotherapy with infusion of hematopoietic stem cells as an innovative approach to the management of women in a poor prognostic group following primary treatment of breast cancer.

RISK ASSESSMENT

An important factor in the decision to advise adjuvant therapy is the risk that the patient faces of recurrent, and ultimately fatal, breast cancer. A patient with a very low risk will have little if any benefit from adjuvant therapy

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and would be exposed to the morbidity and even some chance of mortality from the treatment without the potential for a better outcome. Hence, an accurate assessment of the individual patient's likelihood of developing a recurrence is a critical aspect of the decision-making process.

The best established determinant of risk of systemic recurrence is the status of the axillary lymph nodes. Patients with no axillary node metastases have a 5-year disease-free survival of 70–80% [3,4], whereas with a single nodal, metastasis it is ~60% and further decreases as the number of nodes with metastatic involvement increases [3]. The prognosis for women with a large number of axillary nodal metastases (10 or more) is ominous, with the majority relapsing within 5 years [5].

The need to know the status of the axillary lymph nodes is a major reason for performing an axillary dissection. If other factors indicate the type of adjuvant therapy that is appropriate for the patient, then the need for an axillary dissection might be questioned.

Although many women with operable breast cancer and no axillary nodal metastases live for many years without cancer, some develop fatal metastatic disease. Efforts have been made to identify those women who will remain free of disease without further therapy (and hence will not benefit from adjuvant treatment) and those who will develop a recurrence and thus might be helped by adjuvant therapy [6]. The size of the primary tumor as measured by the pathologist has prognostic value. Lesions <1 cm in maximum dimension are generally associated with an excellent prognosis (10-year survival in the range of 90%) [7]. The histological grade of the tumor, particularly when assigned after applying standardized criteria, has been used to determine prognostic groups. Patients with low grade tumors have a superior outcome to those with high grade tumors [8]. A small contribution to prognosis may come from the hormone receptor status with tumors that are estrogen receptor positive having a slightly lower chance of recurring than those that are negative [6]. Other factors such as the S-phase fraction, ploidy status, and cathepsin D levels have been demonstrated to have predictive value in individual series, but their utility has not always been confirmed in other studies. With the introduction of multiple prognostic factors into patient assessment, a further problem is the manner in which they should be combined to arrive at an overall estimate of outcome. Some investigators have combined factors in formulae to derive a numerical index that can be used to classify a patient's risk of recurrence [9]. Further large prospective studies will help in determining the validity of these approaches.

Participants at a recent consensus conference proposed that women with breast cancer and no axillary nodal metastases were at low risk of recurrence when the tumor was <1 cm in diameter, was estrogen receptor positive, and had a low histological grade. A group with a good prognosis were those patients with a primary lesion of 1–2 cm in maximum diameter, positive for estrogen receptors, and intermediate histological grade. The high risk group had at least one of the following characteristics: size >2 cm, absent estrogen receptors, and high histological grade [10].

RISK-BENEFIT AND COST-EFFECTIVENESS ISSUES

The decision to advise systemic adjuvant therapy is influenced by the relationship between the risks of the proposed treatment and the potential benefits of delayed recurrence and prolonged survival. Other concerns that may come into consideration are costs and the impact on quality of life.

The patient's risk of systemic recurrence following breast cancer surgery varies depending on the factors considered in the previous section. Although the relative benefit of adjuvant therapy may be the same in each risk group, the absolute benefit will differ and will be greater for patients with a higher likelihood of recurrence [11,12]. Thus for women with a low likelihood of recurrence, the difference in survival for the group receiving adjuvant therapy would be expected to be very small. A consensus panel of physicians agreed that adjuvant therapy was not indicated for women predicted to have a lower than 10% mortality at 10 years [10]. However, patients may be willing to undergo treatments with a lower expectation of benefit than are physicians and other health care workers [13], indicating the need for involvement of the patient in decision making. The toxicities of treatment are always a concern, but become increasingly important as the likelihood of benefit decreases. The side effects of chemotherapy may be difficult to justify if the potential benefit is small, whereas the generally low toxicity profile of tamoxifen might support its use in patients with a lower likelihood of benefit.

Although the toxicity of adjuvant therapy is well characterized, few of the published clinical trials have included measures of the impact of such treatment on quality of life [14]. More information in this area would help in providing patients with guidance on the overall impact of adjuvant therapy.

The cost of medical care is of increasing importance to patients, physicians, and society in general. Analyses demonstrate that the costs of adjuvant therapy are in the same range as those for hemodialysis and coronary artery bypass grafting [15]. The role that health maintenance organizations and other third party payers will play in determining standards of care in adjuvant therapy is yet to be seen. Insurance companies already have a major role in controlling patients' eligibility for high dose chemotherapy/hematopoietic stem cell rescue programs that are described later.

ADJUVANT THERAPY IN PREMENOPAUSAL WOMEN

A landmark work by Bonnadonna et al. [16], published in 1976, demonstrated the effectiveness of adjuvant chemotherapy in premenopausal women with axillary nodal metastases using a regimen of cyclophosphamide, methotrexate, and 5-fluorouracil. The benefits were maintained 20 years later [17]. However, even after two decades, patients in both the treated and control arms continued to die of recurrent breast cancer. The Early Breast Cancer Trialists [2] performed a meta-analysis of studies evaluating chemotherapy in women <50 years and confirmed the effects of chemotherapy in improving survival. Thus adjuvant chemotherapy is an appropriate recommendation for premenopausal women at high risk for recurrence based on the presence of axillary nodal metastases or features of the primary lesion (size, tumor grade, and hormone receptors).

There is agreement that adjuvant chemotherapy with a multiagent regimen is a reasonable recommendation for premenopausal women at high risk of recurrence, but the best regimen is not known. Certainly none are ideal in that the degree of benefit is relatively modest and side effects may be significant. The value of regimens including doxorubicin or paclitaxel, or more intensive programs that incorporate higher doses, sometimes in conjunction with growth factors, continues to be evaluated. Some oncologists would employ these programs in patients with particularly ominous prognostic features. However, it would be ideal to enroll such patients in clinical trials in order to assess the efficacy of these programs and provide information to guide treatment decisions in the future. Innovative approaches to the therapy of women at very high risk of recurrence (10 or more positive axillary nodes) are addressed in later under High Dose Chemotherapy.

The side effects of chemotherapy include nausea, alopecia, mucositis, and depression of blood counts. The latter usually account for the life-threatening complications of chemotherapy as a result of infections occurring during neutropenia. In most series mortality is <1% [16,18]. An important consideration in premenopausal women is induction of amenorrhea due to ovarian damage by the chemotherapy. In general, older women near the expected age of menopause are more likely to have chemotherapy-induced amenorrhea than are younger women [19]. However, ovarian dysfunction must be presented as a possible complication for any menstruating woman who is considering adjuvant chemotherapy. The amenorrhea is usually permanent with obvious implications for fertility, a particular concern for women who have delayed child-bearing and are nulliparous. In addition, beginning menopause years earlier than would have occurred in the normal course of events may increase a woman's likelihood of osteoporosis and coronary artery disease [20]. Since hormone replacement therapy is generally considered to be contraindicated following breast cancer, other approaches to reducing these sequelae of menopause must be considered.

Support for the use of tamoxifen as adjuvant therapy in premenopausal women with axillary node negative tumors that are estrogen receptor positive comes from the National Surgical Adjuvant Breast Program (NSABP) study B-14, which demonstrated an improved outcome for women taking tamoxifen in comparison to those taking a placebo [21]. A consensus conference has concluded that tamoxifen could be considered a routine treatment for premenopausal women in the good risk category on the basis of primary <2 cm diameter, the presence of estrogen receptors, low histological grade, and lack of axillary nodal metastases [10].

Improved survival for premenopausal women who had ovarian ablation as an adjuvant treatment was demonstrated in the overview meta-analysis [2]. Elimination of ovarian hormone production by surgical oophorectomy, or by administration of gonadotropin-releasing hormone analogues is being evaluated in clinical trials. The role of this form of therapy, alone or in combination with other adjuvant treatments, is being defined.

ADJUVANT THERAPY IN POSTMENOPAUSAL WOMEN

Tamoxifen is an effective form of systemic adjuvant therapy for postmenopausal women whose tumor is hormone receptor positive [2]. Adjuvant therapy with tamoxifen is a reasonable recommendation for all but those women in whom the risk of recurrence is low and where no adjuvant therapy is advised [10]. Since many patients with a high risk of recurrence will die of breast cancer despite taking tamoxifen, investigators have evaluated combinations of chemotherapy with tamoxifen in this group of patients. Some studies showed a benefit from the addition of chemotherapy to tamoxifen, whereas others showed no additional benefit. The results of the Early Breast Cancer Trialists' Collaborative Group published in 1992 showed a better outcome for women who received chemotherapy and tamoxifen in comparison to tamoxifen alone [2]. Still to be resolved is the clinical significance of the degree of benefit since the toxicity of the combined chemotherapy and tamoxifen is higher than for tamoxifen alone.

The optimal duration of tamoxifen administration is being determined. Recent abstract presentations indicate that 5 years is superior to 2 years [22] and that there is no benefit in continuing beyond five years [23].

The most common side effects of tamoxifen are hot flashes (64% vs. 48% in placebo) and vaginal discharge (30% vs. 15% placebo). An increased rate of deep vein thrombosis in the tamoxifen-treated patients compared to

the placebo controls was observed in the NSABP trial B-14, with one death from a pulmonary embolism [21]. Endometrial cancer also has been observed in postmenopausal women who have been treated with tamoxifen [24]. The extent of risk is still to be defined. Women who are treated with tamoxifen should have an annual gynecological evaluation and should be evaluated promptly if they develop vaginal bleeding. The value of incorporating transvaginal sonography and endometrial biopsies into the monitoring program is yet to be demonstrated.

Postmenopausal patients whose tumors are estrogen receptor negative and who are at risk for recurrence benefit from chemotherapy, especially if they are $<$ age 60. The benefit is less than that for premenopausal women [2].

The arbitrary exclusion of older postmenopausal women from the early clinical trials of adjuvant therapy (age limits of 65 or 70 years were common) has resulted in limited published experience on the use of adjuvant therapy in this group of patients.

HIGH DOSE CHEMOTHERAPY WITH HEMATOPOIETIC STEM CELL RESCUE

Although the outcome for women with operable breast cancer has improved with adjuvant therapy, many still die of recurrent breast cancer. Thus new adjuvant programs are necessary, particularly for those women who have a large number of axillary node metastases ($\geq$10) or large primary lesions ($\geq$5 cm) and are therefore at high risk for metastatic disease. The impetus to employ high dose chemotherapy with stem cell support in the adjuvant setting comes from the initial trials in patients with metastatic breast cancer that demonstrated the feasibility of this approach [25] and with improvements in the procedure, including routine use of hematopoietic growth factors, which have markedly reduced the mortality rate.

Experimental and clinical observations provide a rationale for high dose chemotherapy in cancer treatment. Laboratory models of breast cancer demonstrate that the delivery of high doses of chemotherapy is central to achieving curative therapy. Tumor recurrence may be due to the emergence of drug-resistant clones, and some components of this resistance can be overcome by escalating the doses of the cytotoxic drugs by 5–10-fold [26,27]. Increasing the dose intensity of treatment has been postulated to correlate with response rates and ultimately disease-free survival [28]. Breast cancer would seem to be an ideal tumor system in which to study high dose chemotherapy because of the dose-response effect and because the limiting toxicity for many of the effective medications is myelosuppression. The infusion of autologous hematopoietic stem cells should permit the safe use of higher doses of marrow toxic chemotherapy by accelerating the rate of recovery from the myelotoxic effects of the drugs.

A number of high dose chemotherapy regimens have been developed with most including cyclophosphamide and a second alkylating agent in addition to other antineoplastic drugs. No regimen has demonstrated superiority over others.

Hematopoietic stem cells from the bone marrow or from the peripheral blood can be harvested and cryopreserved for infusion following the administration of the chemotherapy. The initial studies employed bone marrow stem cells alone. Subsequent clinical trials used a combination of marrow and peripheral blood stem cells. The use of peripheral blood progenitors results in a more rapid hematological recovery compared to bone marrow alone with a resultant decrease in morbidity and mortality. This improved outcome is reflected in the results reported to the North American Bone Marrow Transplant Registry. In 1989, the majority (79%) of autotransplants used bone marrow alone as stem cell source and 100-day mortality was reported as 22%. In 1994, 78% of autotransplants used a peripheral blood stem cell source with a concomitant drop in the mortality to 2% nationwide. Currently, many patients will receive only stem cells from peripheral blood without bone marrow. The elimination of the bone marrow harvest simplifies the overall procedure and reduces costs.

A concern with autologous transplantation is the harvesting and cryopreservation of breast cancer cells along with the stem cells [29–31]. Although the degree of contamination with tumor cells is less with peripheral blood stem cell preparations than with bone marrow, viable malignant cells are present in both sources of hematopoietic stem cells as assessed by in vitro techniques [31,32]. Thus efforts have been made to minimize the number of tumor cells re-infused by processing the stem cell preparation in vitro to destroy cancer cells or to concentrate the stem cells in a fraction with a decreased number of cancer cells [33]. The importance of this manipulation is not known since the clinical relevance of tumor cell contamination itself is not clear. Whereas gene marking studies have demonstrated relapse due to contamination of progenitor cell infusion in leukemia and neuroblastoma [34], analogous studies are lacking that prove that recurrent breast cancer following high dose chemotherapy/stem cell rescue is due to the infusion of contaminating tumor cells with the hematopoietic precursors and not to regrowth of residual cancer cells, which were able to survive the high dose chemotherapy.

The toxicities of high dose chemotherapy are similar to those with conventional dose but, as expected, are more severe. Acute toxicities include nausea, vomiting, diarrhea, and mucositis. Although the duration of marrow suppression is reduced with the hematopoietic stem cells and growth factors, all patients go through a period of

profound leukopenia and thrombocytopenia. Most patients will become febrile and require antibiotic treatment. Platelet transfusions are almost universally necessary. With higher doses of chemotherapy, side effects that are uncommon at conventional doses may develop such as cardiomyopathy with cyclophosphamide.

Patients receiving high dose chemotherapy/stem cell rescue have been reported to have a better outcome in comparison to historical controls [35]. It has been suggested that the difference in survival can be explained solely on the basis of patient selection. The screening workup for patients being considered for a high dose chemotherapy protocol is exhaustive with more imaging studies and other evaluations than are conventionally performed in patients about to begin adjuvant chemotherapy. As a result of this testing, some patients will be found to have metastatic disease and not proceed in the adjuvant program. In contrast, the historical control group that had not been subjected to such a rigorous assessment will include some individuals with metastatic disease who would be expected to have a higher rate of clinical relapse. This criticism of results from single institutions employing historical comparisons underlines the importance of the ongoing prospective randomized trials.

CONCLUSION

Systemic adjuvant therapy represents a major advance in the management of breast cancer and is now an established component of the treatment for many women with this illness. The range of possible recommendations requires that each patient be assessed individually and that she understand the risks and benefits of her options. The relapse of some patients despite adjuvant therapy underscores the importance of asking patients to enter clinical trials that are evaluating new approaches to treatment. The results of such studies will increase the knowledge that can be used in advising patients on their best course of action.

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